REMARKS

Claims 2-7 and 9 are pending in the instant application. Claims 2 and 3 have been amended to indicate that EPO can be used to enhance the function of "central nervous system" tissue in a mammal and thereby enhance the associative learning and cognitive function in/of the mammal. Support for the amendment is found at page 8, lines 19-21 and page 20, lines 11-14. No new matter has been added by these amendments.

Entry of the amendments and the remarks made herein into the record of the above-identified application is respectfully requested. Applicants believe that the amendments and remarks made herein place all pending claims in condition for allowance.

THE REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, FOR LACK OF ENABLEMENT SHOULD BE WITHDRAWN

Claims 2-7, and 9 are rejected under 35 U.S.C. § 112, first paragraph. The Examiner contends that claims 2 and 3 are enabled for *normal, damaged or injured excitable tissue* in a mammal, *wherein the damage or injury is caused by stroke*, but the claimed methods are not enabled for the full scope of enhancing the function of *damaged or injured excitable tissue* in general. The Examiner contends that Applicants support for enhancement of function, *i.e.* associative learning/cognitive function, in one instance of damaged/injured tissue is not supportive of a genus of "unlimited number" of conditions and diseases with damaged/injured excitable tissue and poor associative learning/memory.

Additionally, The Examiner contends that claims 4-7 and 9 are enabled for *normal, damaged or injured excitable tissue* in a mammal, *wherein the damage or injury is caused by stroke, diabetic neuropathy or autoimmune encephalomyelitis*, but the claimed methods are not

enabled for the full scope of enhancing the function of *damaged or injured excitable tissue* in general. The Examiner contends that Applicants support for enhancement of function in two examples (diabetic neuropathy and autoimmune encephalomyelitis) of damaged/injured tissue is not supportive of a genus of "unlimited number" of conditions and diseases with damaged/injured excitable tissue and poor associative learning/memory.

Applicants respectfully disagree. With respect to the use of peripherally administered EPO to enhancing the function of damaged excitable tissue, enhance associative learning and/or cognitive function in a mammal, Applicants invite the Examiner's attention to the following studies published subsequent to the filing date of the present application which demonstrate that the claimed methods are enabled:

(1) Lu *et al.,* 2005, Journal of Neurotrauma 22(9):1011-1017 ("Lu") (Reference FF)

(2) Mogensen *et al.,* 2004, Pharmacology, Biochemistry and behavior 77:381-390 ("Mogensen ") (Reference FG);

(3) Kumral *et al.,* 2004, Behavioral Brain Res. 153:77-86 ("Kumral") (Reference FH);

(4) Ehrenreich *et al.*, Molecular Psychiatry (2003), 1-13 ("Ehrenreich") (Reference FI);

(5) van der Meer *et al.*, 2005, JACC 46(1): 125-33 ("van der Meer") (Reference FJ); and

(6) Keswani *et al.*, 2004, Ann Neurol 56:815-826 ("Keswani") (Reference FK).

Lu analyzed the effects of EPO on cognitive function following a traumatic brain injury. Two groups of rats were evaluated the first group was peripherally administered high doses of EPO (5000 U/kg EPO) for 14 days after rats were injured using a controlled cortical impact model of traumatic brain injury, with the first dose being administered one day following. The second group was administered saline instead. The animals were trained in a modified Morris

Water Maze test – a platform was randomly placed within the NE quadrant of a Morris Water Maze test apparatus and the amount of time rat spent in NE quadrant in relation to total time spent in water maze was recorded – for five days with two days rest prior to traumatic brain injury. Following traumatic brain injury the animals were tested on days 1, 4, 8, and 15 following the injury. Figure 1 on page 1013 represents the results of testing and indicates that the rats treated with EPO spent a greater portion of their time within the correct quadrant. Lu noted that the EPO administration reduced the spatial learning dysfunction experienced within the rats due to the traumatic brain injury. *See* Lu, pg.1013, col. 2 section entitled "Erythropoietin Enhances the Restoration of Spatial Memory". Thus, the results demonstrate that the peripheral administration of effective doses of EPO effectively enhanced the function of damaged excitable central nervous system tissue, thereby enhancing associative learning and cognitive function in rats with damaged excitable tissue.

Mogensen shows that peripherally administered EPO significantly improved the function in a place learning task of rats subjected to transection of the fimbria-fornix. Hippocampal lesions in rats, such as those generated by transection of the fimbria-fornix, have been repeatedly associated with impaired acquisition of water-maze-based place learning of the allocentric mapping type. Forty rats were used in the study divided into four groups: (1) Sham surgery treated with saline, (2) sham surgery treated with EPO (5,000 U/kg), (3) bilateral transaction of the fimbria-fornix treated with saline, and (4) bilateral trisection of the fimbria-fornix treated with EPO (5,000 U/kg). All groups were treated at the time of surgery. Six to seven days following the operation the rats were tested in a Morris Water Maze for 25 days with five trials per day. The rats were evaluated for: (1) total swim distance, (2) the total duration of a swim, (3) the average speed of the swim, (4) the "mean distance to the platform," (5) the "heading angle error,"

and (6) the percentage of the swim duration during which the animal was found in the outer maze centered annulus. Figures 1-3 and Tables 1-3 tally the results of the rat trials in the Morris Water Maze. Mogesen noted that the fibria-fornix group that was treated with EPO had a more transient and limited impairment in comparison to the saline treated fibria-fornix group. Mogosen further noted that EPO "supports and enhances the training-induced functional recovery" in the fibria-fornix group. *See* Mogesen, pg. 388, col. 1. Thus, the results demonstrate to one of ordinary skill in the art that the peripheral administration of effective doses of EPO effectively enhanced the function of damaged excitable central nervous system tissue, thereby enhancing associative learning and cognitive function in rats with damaged excitable tissue.

Kumral demonstrated that EPO treatment immediately after inducing hypoxia-ischemic brain injury in rat pups led to improved long-term neurobehavioral achievements. As is noted within Kumral, this type of injury is associated with neonatal mortality, and subsequent sequelae such as cerebral palsy, mental retardation, learning disability, and epilepsy. See Kumral, pg. 77. In this experiment, fourteen rat pups underwent permanent unilateral carotid ligation followed by 2 hour recovery and 2.5 hour period of hypoxia (92% N_2, 8% O_2). Another seven pups underwent a sham operation and another seven were retained as a control. After the period of hypoxia, seven pups were treated with EPO (1000 U/kg) intraperitoneally and the remaining seven pups were treated with saline intraperitoneally. All of the rats were evaluated in the Morris Water Maze at the third week following surgery (4 days a week, four times a day, and one day probe trials) and at 20 weeks following surgery (4 days a week, four times a day and one day probe trials), illustrated in Fig. 1, pg. 78. The escape latency, *i.e.* the time lapsed before the rat reaches the platform, was recorded for each rat as well as the time spent in the relevant quadrant by the rat during probe trials. The results of these trials are illustrated in Figs. 2, 3, and 5. Kumral noted that EPO

significantly improved the water maze impairment in rats exposed to neonatal hypoxic-ischemic brain injury. *See* Kumral, pg.80, col. 1, section 3.1, and pg. 81, col. 1. Thus, the results demonstrate that the peripheral administration of effective doses of EPO effectively enhanced the function of damaged excitable central nervous system tissue, thereby enhancing associative learning and cognitive function in rats with damaged excitable tissue.

Ehrenreich, a reference co-authored by the Applicants, argues the benefit of the use of EPO to enhance cognitive brain function within schizophrenic patients. Ehrenreich utilizes the results of rodent studies, primary hippocampal neurons in culture, immunohistochemical analysis of human post mortem brain tissue and nuclear imaging technology to demonstrate: (1) the peripherally administered rhEPO crosses the blood brain barrier, (2) rhEPO is enriched intracranially in healthy men and to a greater extent in schizophrenic patients, (3) EPO receptors are densely expressed in the hippocampus and cortex of schizophrenic patients and less so in controls, and (4) peripherally administered EPO enhances cognitive function in mice in the context of a taste aversion task involving the cortical and subcortical pathways presumably affected in schizophrenia (*See* Ehrenreich, pg. 2, col. 1 & Example 2 in current application). Ehrenreich draws the conclusion that "[t]he positive results obtained with rhEPO in this context (conditioned taste aversion) encourage pilot trials of rhEPO in schizophrenia since comaparable properties are thought to be affected in this disease." Ehrenreich, pg. 10, col. 1. Thus, Ehrenreich demonstrates to one skilled in the art that the results of the conditioned taste aversion model in rats indicate that the peripheral administration of effective doses of EPO may effectively enhanced the function of damaged excitable central nervous system tissue, thereby enhancing associative learning and cognitive function in rats with damaged excitable tissue is diseases using similar pathways, such as schizophrenia.

Van der Meer illustrated that EPO enhances cardiac function in a rat model of post-myocardial infarction ("MI"). In this particular model, rats underwent coronary ligation or sham surgery. The rats that underwent coronary ligation were then divided into three groups: (1) untreated MI, (2) a single bolus of EPO following MI, (3) a single bolus of EPO following MI and once every three weeks, and (4) EPO treatment beginning three weeks after MI and once every three weeks. Nine weeks after the MI, the cardiac function of the rats was evaluated by inserting a microtip pressure transducer into the left ventricular cavity and measuring heart rate, left ventricular systolic pressure (LVSP), left ventricular end-diastolic pressure (LVEDP), and developed left ventricular end-diastolic pressure. The maximal rates of increase and decrease in left ventricular pressure were determined. Additionally, the microtip pressure transducer was withdrawn into the aortic arch and the arterial systolic and diastolic blood pressures were measured. The results of these measurements are noted in Table 1 and Fig. 1 depicts the results of EPO treatment on hemodynamic parameters. Van der Meer noted that the administration of EPO beginning 3 weeks following the injury "results in an improved cardiac function, as shown by a 17% increase in dLVP at 34% reduction in LVEDP." van der Meer, pg. 129, col. 2. Thus, van der Meer demonstrates to one of ordinary skill in the art that the peripheral administration of effective doses of EPO effectively enhanced the function of damaged excitable cardiac tissue, caused by disease.

Keswani examines the effects of peripherally administered EPO on axonal degeneration. Axonal degeneration is associated with peripheral neuropathies, such as diabetic and human immune deficiency virus sensory neuropathies. Keswani induced neuropathy in Sprague-Dawley rats by administering acrylamide in their drinking water at a concentration of 400ppm for 2 weeks. The rats were then divided into three groups: (1) rats receiving daily intraperitoneal administration

of EPO (2,500 IU/kg) for three weeks, (2) rats receiving daily intraperitoneal administration of EPO for three weeks; and (3) a control group. The rats were tested for motor strength using grip strength measurements and for mechanical hypo/hyperalgesia using von Frey filaments. The results of these tests are detailed in Fig. 5 (b) and (d), Keswani, pg. 823. Keswani noted that the EPO treated animals had both an improved mechanical hyperalgesia on von Frey filament testing and greater grip strength. Keswani, pg. 822. Thus, Keswani demonstrates to one of ordinary skill in the art that the peripheral administration of effective doses of EPO effectively enhanced the function of damaged excitable peripheral nervous system tissue, tissue experiencing axonal degeneration specifically.

The experimental results described above demonstrate the efficacy of the claimed methods in animal models, and in human subjects, for a number of different conditions involving tissue damage as a result of various diseases. Thus the claims are enabled and the rejection under 35 U.S.C § 112 should be withdrawn.

THE REJECTIONS UNDER THE DOCTRINE OF OBVIOUSNESS-TYPE DOUBLE PATENTING SHOULD BE WITHDRAWN

The Examiner has provisionally rejected claims 5-7 and 9 for obviousness-type double patenting in light of co-pending Application No. 09/717,053; and provisionally rejected claims 4-7 and 9 for obviousness-type patenting in light of 09/716,960.

While Applicants do not agree with the propriety of these rejections, Applicants concurrently submit terminal disclaimers to obviate the rejection.

CONCLUSION

Entry of the foregoing amendments and remarks into the record of the above identified application is respectfully requested. Applicants estimate that the remarks made herein place the pending claims in condition for allowance. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

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